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Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults ☆

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ABSTRACT

Background: Hepatitis B virus infection remains an important public health problem in the United States. Currently approved alum-adjuvanted vaccines require three doses and have reduced immunogenicity in adults, particularly in those who have diabetes mellitus, or are older, male, obese, or who smoke.
Methods: Phase 3 observer–blinded, randomized (2:1 HBsAg-1018 [HEPLISAV-B™]:HBsAg-Eng [Engerix-B®]), active–controlled trial in adults 18–70 years of age. HBsAg-1018 was administered intramuscularly at weeks 0 and 4 and placebo at week 24 and HBsAg-Eng at weeks 0, 4, and 24. The primary immunogenicity endpoint assessed the noninferiority of the seroprotection rate at week 28 in participants with type 2 diabetes mellitus. Secondary endpoints included seroprotection rates in the total trial population and by age, sex, body mass index, and smoking status.
Results: Among 8374 participants randomized, 961 participants in the per-protocol population had type 2 diabetes mellitus. In diabetes participants, the seroprotection rate in the HBsAg-1018 group at week 28 was 90.0%, compared with 65.1% in the HBsAg-Eng group, with a difference of 24.9% (95% CI: 19.3%, 30.7%), which met the prospectively-defined criteria for noninferiority and statistical significance. In the total study per-protocol population (N = 6826) and each pre-specified subpopulation, the seroprotection rate in the HBsAg-1018 group was statistically significantly higher than in the HBsAg-Eng group.
Conclusion: Two doses of HBsAg-1018, administered over 4 weeks, induced significantly higher seroprotection rates than three doses of HBsAg-Eng, given over 24 weeks, in adults with factors known to reduce the immune response to hepatitis B vaccines as well as in those without those factors. With fewer doses in a shorter time, and greater immunogenicity, HBsAg-1018 has the potential to significantly improve protection against hepatitis B in adults at risk for hepatitis B infection.

☆ HEPLISAV-B was approved for use in adults in the United States on November 9, 2017.

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1. Introduction

Hepatitis B virus (HBV) infection is a major public health problem globally including the United States (US). Worldwide, an estimated 257 million persons are living with chronic hepatitis B infection and an estimated 887,000 persons died in 2015 from complications of hepatitis B [1]. In the US, up to 2.2 million individuals are chronically infected with HBV [2] and an estimated 5000 individuals die from HBV complications each year [3].

In the US, the Centers for Disease Control and Prevention (CDC) estimated there were approximately 21,900 new HBV infections in 2015 with the vast majority of cases occurring in adults [4]. Despite the availability of vaccines for HBV, rates of acute hepatitis B infection have recently increased in the US [4]. In fact, CDC has reported a recent 114% increase in acute hepatitis B cases in Kentucky, Tennessee, and West Virginia associated with injection drug use stemming from the ongoing opioid epidemic [5].

Ongoing HBV infections in adults can be attributed to the challenges of vaccinating adults at risk of infection [6,7] and the limitations of the currently approved vaccines (Engerix-B® [HBsAg-Eng] and Recombivax®). The currently approved vaccines: (1) have reduced immunologic responses in older adults, men, individuals with diabetes mellitus, obese individuals, and smokers [8–18]; (2) require adherence to a 3-dose vaccination schedule over 6 months [19]; and, (3) have a prolonged time before development of seroprotection (ie, >6 months) [19] in many recipients.

In the US, individuals with diabetes mellitus have approximately twice the risk of HBV infection and those who contract HBV have higher rates of complications including acute symptomatic hepatitis, chronic HBV infection, hepatocellular carcinoma, and death compared to individuals without diabetes [20–22]. In 2011, CDC's Advisory Committee on Immunization Practices recommended that in the US, hepatitis B vaccination be routinely administered to all unvaccinated adults with diabetes <60 years of age and to unvaccinated adults with diabetes who are ≥60 years of age at the discretion of the treating clinician [22]. Since the recommendations were released, little progress has been made in vaccinating persons with diabetes [23,24].

HBsAg-1018 (HEPLISAV-B™) is a hepatitis B vaccine developed by Dynavax Technologies Corporation (Berkeley, CA) that utilizes a cytidine-phosphate-guanosine oligodeoxynucleotide (CpG-ODN), 1018, as an adjuvant. CpG-ODNs bind Toll-like receptor 9 (TLR9), an innate immune system pattern recognition receptor for DNA expressed predominantly in plasmacytoid dendritic cells [25]. 1018 stimulates a directed immune response to hepatitis B surface antigen (HBsAg) instead of the multi-pathway, broad immunostimulatory response induced by alum [26]. HBsAg-1018 has induced significantly higher and earlier seroprotection rates in healthy adults in two previous phase 3 trials [27,28]. HBsAg-1018 was licensed by the US Food and Drug Administration (FDA) for use in adults in the US on November 9, 2017.

In this trial of 8374 adults, the immunogenicity and safety of HBsAg-1018 were compared to the most commonly used licensed hepatitis B vaccine, HBsAg-Eng, in populations known to have good responses (young adults, women, persons without diabetes, non-obese, and non-smokers) and in populations known to have reduced rates of seroprotection (eg, older adults, men, persons with diabetes, the obese, and smokers). To evaluate immunogenicity in persons with diabetes recommended for routine vaccination by ACIP, the primary immunogenicity endpoint in this study was in participants with diabetes. Secondary endpoints were seroprotection rates in the total study population and by factors associated with reduced seroprotection rates from the alum adjuvanted vaccines.

2. Materials and methods

This was a phase 3, observer-blinded, randomized, active-controlled (HBsAg-Eng) trial of the immunogenicity and safety of HBsAg-1018 in adults 18 to 70 years of age. Safety will be reported in another paper. The study was conducted at 40 study sites in the US between April 2014 and October 2015. A central institutional review board approved the protocol and the trial was conducted according to the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained prior to enrollment.

2.1. Key trial objectives

Co-primary objectives comprised the overall safety of HBsAg-1018 with respect to clinically significant events and an immunogenicity objective to demonstrate the noninferiority of the seroprotection rate (SPR) of HBsAg-1018 compared with the SPR of HBsAg-Eng among adults with type 2 diabetes mellitus at 4 weeks following the last dose of HBsAg-Eng (week 28). SPR was defined as the proportion of participants with antibody to hepatitis B surface antigen [anti-HBs] ≥ 10 mIU/mL. Diabetes mellitus was defined as having a clinical diagnosis of type 2 diabetes mellitus and taking at least an oral or non-insulin injectable hypoglycemic agent and/or insulin. Key secondary objectives were to demonstrate noninferiority of the SPR at week 24 induced by HBsAg-1018 to the SPR at week 28 induced by HBsAg-Eng in the total study population and in the following subgroups: by age, sex, body mass index (BMI), and smoking status, and if noninferiority was established, to demonstrate that the SPR induced by HBsAg-1018 was statistically significantly higher than that induced by HBsAg-Eng. All immunogenicity endpoints are based on the previous phase 3 trials that showed that the peak SPR among persons with type 2 diabetes mellitus was at 28 weeks for both vaccines, and the peak SPR among those without diabetes was at 24 weeks for HBsAg-1018 and 28 weeks for HBsAg-Eng.

2.2. Study population

Eligible participants were adults 18 through 70 years of age who were seronegative for HBsAg, anti-HBs, antibody against hepatitis B core antigen (anti-HBc), and human immunodeficiency virus. Participants were excluded from the trial if they: were pregnant, breastfeeding, or planning a pregnancy during the study; had a history of HBV infection or autoimmune disease; were taking chronic corticosteroid therapy; had previously received any hepatitis B vaccine (approved or investigational), DNA plasmid, or oligonucleotide; or had any condition that in the opinion of the investigator would interfere with compliance or interpretation of the study assessments.

2.3. Study vaccines and administration

HBsAg-1018 (HEPLISAV-B manufactured for Dynavax Technologies Corporation, Berkeley, California by Rentschler Biotechnologie GmbH, Laupheim, Germany) consists of 20 mcg of yeast-derived recombinant HBsAg (subtype *adw*) and 3000 mcg of 1018 adjuvant per 0.5 mL dose and was administered by intramuscular injection in the deltoid muscle at weeks 0 and 4. Saline placebo was administered as the third injection at week 24 to maintain blinding.

HBsAg-Eng (Engerix-B, GlaxoSmithKline Biologicals, Rixensart, Belgium) consists of 20 mcg of recombinant HBsAg combined with 500 mcg of aluminum hydroxide (alum) adjuvant per 1.0 mL dose. Participants in the HBsAg-Eng group received the FDA approved regimen of intramuscular injections at weeks 0, 4, and 24.

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